Remarks/Arguments

Claims 1-15 and 17 are pending in the application. Claims 1-9 and 15 have been withdrawn from consideration pursuant to a lack of unity objection. Claims 10-14 and 17 are therefore under consideration. Reconsideration is requested in view of the above changes and the following remarks.

The terminology "vaccine composition" in the pending claims has been changed to "a composition for inducing an immune response to a pathogenic bacteria". It is apparent from the specification that the compositions of the invention have this effect. Support for induction of an immune response to a pathogenic organism is provided, for example, at page 8, lines 1-10.

The feature of the "in-situ" production has been inserted into the claims as describing the formation of complexes between a heat shock protein and an antigenic peptide, to emphasize that the heat shock protein - antigenic peptide fragment complex is produced within the bacterial pathogen cell. Bases for this feature is derived from claim 17 as originally filed, and from the specification page 16, line 26 and 27.

The claims have been further amended to point out that the production of the induced heat shock protein results from the exposure of the pathogenic bacteria to a stress-inducing heat shock stimulus. Support in the speciation may be found at page 6, line 16, which refers to exposing the pathogen to stress inducing stimuli, such as heat. Further support for the application of heat stress can be derived from page 9, lines 8 to 11.

The claims have been amended to point out that the formation of complexes between heat shock proteins and an antigenic peptide fragment derived from pathogenic bacteria is accomplished by an ATP-dependent reaction. This feature is supported by the specification at page 3, lines 4 to 7.

Response to Section 112, 1st paragraph Rejection

Claims 10-14 and 17 have been rejected for lack of enabling disclosure in the specification. Examiner submits that the immune response of the present invention is not enabled for vaccines and the induction of a protective immune response.

Claims 10 and 11 as amended are directed to compositions for inducing an immune response. As acknowledged by the examiner in the official action, the instant specification describes, teaches and shows the induction of an immune response to heat shock protein/peptide complexes. Specifically, as noted by the Examiner, Example 2 of the instant specification clearly shows the induction of an immune response. Applicant further submits that Examples 3 and 4 of the instant specification show the induction of further immune responses as evidenced by the production of a specific antibody response.

In relation to Examiner's further rejection that the method of obtaining the claimed heat shock protein/peptide complex is not limited to the production of the claimed composition by heat, Applicant submits that the amendment to claims 10 and 11 to recite the specific requirement of exposing the pathogenic bacteria to a stress-inducing heat shock stimuli renders this rejection moot.

Examiner states that "the specification fails to provide an adequate written description of what antigenic fragment peptides when associated with a heat shock protein would induce a protective immune response when administered to an animal". Applicant respectfully submits that the present invention does not require the skilled person to select, or require to select the antigenic peptide fragment which is complexed to the heat shock protein. As described in the instant specification, particularly with reference to Examples 3 and 4, and further at page 9, lines 17 to 27, the stress stimuli applied to the pathogenic bacteria serves to induce the production of a subset of heat shock proteins which complex with antigenic fragments which mediate increased immune responses when administered to a host. It is a specific, desirable advantage of the

present invention that there is no need to identify specific antigenic peptide fragments to associate with the heat shock protein in order to mediate an immune response. Specifically, the heat shock proteins which are induced following heat stressing of the bacteria bind to a broad spectrum of antigenic peptides which are present within the cell. In turn these complexes can be administered to a host in order to induce a protective immune response against the bacterial pathogen from which the heat shock protein/antigenic peptide fragment complex has been derived. The fact that the heat shock protein associates with different peptide fragments serves to allow the host to be exposed to a number of antigenic peptide fragments which are derived from the pathogenic bacteria. As such, the immune response which is mounted when the heat shock protein/antigenic peptide fragment complexes are administered to an individual serve to result in the immune response of the host being directed to a broad spectrum of antigenic peptides and antigenic epitopes. The resulting immune response therefore is far superior to that obtained when a host is responding against a single, specifically selected antigen derived from a pathogen.

Furthermore, as illustrated in Examples 3 and 4, the induced heat shock proteins associate with antigenic peptide fragments which are shown to mediate an effective immune response in the host. Thus, this provides further basis to show that the skilled person need not be concerned with the identification nor isolation of specific antigenic peptide fragments, but rather need only obtain complexes of heat shock/antigenic peptide fragments in order to induce an immune response. In this regard, Applicant submits that there is adequate teaching provided in the instant Specification to allow the skilled person to undertake such activities and actions. Accordingly Applicant submits that undue experimentation need be undertaken by the skilled person in order to perform the instant invention.

Response to Section 102 Rejections

Laminet et al.

Examiner has maintained the objection against claims 10, 11 and 13 under 35 U.S.C. 102(b) as allegedly being anticipated by Laminet et al. (EMBO Journal. 1990. 9(7): 2315-2319).

Applicant submits that the amendment of claim 10 and claim 11 such that they require the use of an induced heat shock protein (which is obtained by the exposing the pathogenic bacteria to a heat shock stress inducing stimuli) recites a feature which is not taught or suggested in Laminet. The constitutively produced heat shock proteins disclosed in Laminet would not fall within the scope of claim 10 or claim 11. Furthermore, the heat shock protein would not bind to the same profile of antigenic peptide fragments as those which would be bound by an induced heat shock protein, as per the comparative examples taught in Example 3 and Example 4.

Claims 10, 11 and 13 are not anticipated by Laminet.

Srivastava (US Patent No 5,961,979)

Claims 10-14 and 17 have been rejected as allegedly anticipated by Srivastava (US Patent No 5,961,979).

Srivastava discloses the formation of a heat shock protein/antigenic peptide fragment which is produced by chemical synthesis. The chemical synthesis results in complexes between heat shock proteins and an antigenic fragment which are not complex *in-situ* within the bacterial cell from which the antigenic fragment is derived and in which the heat shock protein has been induced.

In order to form a "stress protein" – peptide complex, Srivastava requires the initial step of identifying the peptide which is to be complexed to the heat shock protein. The peptide can be "any amino acid sequence that is present in a eukaryotic cell infected with an intracellular pathogen but not present when the cell is not infected with the same pathogen". This peptide need then be identified and complexed to a recombinant heat shock protein. The methods of Srivastava are therefore limited firstly by limiting to allowing antigens which are selected from intracellular bacteria, and secondly, limited to only a *single* antigen being selected to which an immune response of the host can be directed in order to confer immunity against the pathogen from which the antigenic peptide fragment is derived. The presently claimed invention allows an immune response to be directed to extracellular bacteria. It does not suffer from the drawback of having to identify and select antigens which are specific to the pathogenic organisms, and further, allows a far broader spectrum of antigenic peptide fragments to be sample (when bound by the heat shock proteins) and thus provides a composition which allows an immune response to be mediated by the host to a number of antigenic peptide fragments derived from the pathogenic bacteria and not to a single pathogenic bacteria which is specifically identified as part of the production procedure.

It is respectfully submitted that claims 10-14 and 17 are not anticipated by Srivastava.

Wallen et al. (US Patent No 5,747,332)

Examiner submits that claims 10, 11 and 13 are anticipated by Wallen et al (US 5,747,332). Examiner submits that Wallen discloses compositions in accordance with the present invention. However, again the production of the heat shock proteins does not result from stressing of the cell by heat shock.

Accordingly, the heat shock protein-peptide complexes which are provided by Wallen are not as immunogenic as the heat shock protein-peptide complexes of the present invention for the reasons presently described.

Furthermore, the method disclosed in Wallen for associating peptides with heat shock protein is not in accordance with that of the present invention and does not produce equivalent heat shock protein-antigenic peptide fragment complexes. The method is described briefly at column 2, line 15 to 23. Briefly, heat shock proteins are bound to an ADP column matrix and a solution of peptides and polypeptides are then added. A buffer is then added to elute the heat shock proteins, which are now complexed to an associated antigenic peptide fragment.

The present claims require that the complexes are formed between a heat shock protein derived from a pathogenic bacteria are complexed in-situ within the bacterial pathogen cell to an antigenic peptide fragment derived from that cell. The association of a heat shock proteins derived from a bacterial pathogen with an antigenic peptide fragment also derived from the same bacterial pathogen, wherein the complex is formed within the cell is not provided for by the present invention.

Examiner makes reference to column 3, lines 49-67 of Wallen as evidence of use of heat shock proteins derived from bacteria. However, there is no mention of the step of heat stressing a cell as a first step in order to achieve the heat shock proteins which bind a subset of antigenic peptide fragments which induce more immunogenic immune responses in a host. This step would be necessary to obtain induced heat shock proteins which are equivalent to those provided by claims 10 and 11 of the present invention.

Claims 10, 11 and 13 are therefore not anticipated by Wallen.

Yokata *et al.*

Claims 10, 11 and 17 have been rejected as allegedly anticipated by Yokata *et al.*

Claim 10 and claim 11 have been amended in order to define that "the formation of the complex between the induced heat shock protein and the antigenic peptide fragment is accomplished in an

ATP-dependent reaction". The expenditure of ATP results from the association of the antigenic peptide fragment with the peptide binding site of the heat shock protein.

In the document of Yokota, a complex between a 60kDa heat shock protein with the beta subunit of the urease enzyme is formed. However the association of the heat shock protein and the beta subunit of the urease enzyme does not occur at the peptide binding site of the heat shock protein and further does not result in ATP being expended.

Claims 10 and 11 require that complexes produced in-situ from the pathogenic bacteria between an induced heat shock protein and an antigenic peptide fragment derived from the pathogenic bacteria are used to induce an immune response. The urease beta subunit does not fall within the requirements of the claims, as they require a heat shock protein to complex with an antigenic peptide fragment derived from the pathogenic bacteria. The urease beta subunit cannot be classified as an antigenic peptide fragment.

Accordingly, it is respectfully submitted that claims 10-11 and 17 are not anticipated by Yokata *et al.*

Eschweiler *et al.*

Claims 10, 11 and 17 have been rejected as allegedly anticipated by Eschweiler *et al.*

Eschweiler discloses a 60k protein which is *predicted* to be a chaperonin. The function of this 60k protein is suggested on page 83 as "most likely supports the transport as well as stabilisation and folding of urease to its external location". There is no teaching of how the 60k associates with the urease.

Based on the submissions of the examiner, it is therefore taken, for the purposes of consideration of this document, that the 60k protein is indeed a heat shock protein. If this is in fact the case,

then the complex which forms between the 60k heat shock protein and the urease would not result in an ATP-dependent reaction, and further, in as far as the claims require the heat shock protein to be bound to an antigenic peptide fragment derived from a pathogenic bacteria, this would not be provided, most specifically because the heat shock protein is bound to the complete urease molecule (or at least the beta subunit), and this is not a fragment. Accordingly, Eschweiler does not teach of all the features of the claims.

For the foregoing reasons, claims 10, 11 and 17 are not anticipated by Eschweiler *et al.*

Austin *et al.*

Claims 10, 11 and 17 have been rejected as allegedly anticipated by Austin *et al.*

Claims 10 and 11 recite the feature that complexes produced *in-situ* from the pathogenic bacteria between an induced heat shock protein and an antigenic peptide fragment derived from the pathogenic bacteria are used to mediate an immune response. The urease beta subunit does not fall within the requirement of the claim, as the claim requires the heat shock protein to complex with an antigenic peptide fragment derived from the pathogenic bacteria. The urease beta subunit cannot be classified as an antigenic peptide fragment. It is submitted that the claims are not disclosed in the teachings of Austin.

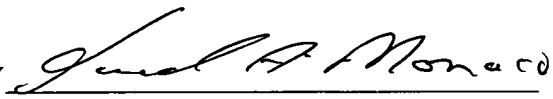
Accordingly it is submitted that claims 10, 11 and 17 are not anticipated by Austin *et al.*

Conclusion

The claims remaining in the application are believed in condition for allowance. An early action toward that end is earnest solicited.

Respectfully submitted

CAMILO ANTHONY LEO SELWYN COLACO

BY 

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